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(54) Title: NOVEL HUMAN PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

The present invention provides novel isolated SECX polynucleotides and the membrane–associated or secreted polypeptides encoded by the SECX polynucleotides. Also provided are the antibodies that immunospecifically bind to a SECX polypeptide or any derivative, variant, mutant or fragment of the SECX polypeptide, polynucleotide or antibody. The invention additionally provides methods in which the SECX polypeptide, polynucleotide and antibody are utilized in the detection and treatment of a broad range of pathological states, as well as to other uses.

NOVEL HUMAN PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

FIELD OF THE INVENTION

The invention relates to polynucleotides and polypeptides encoded by such polynucleotides, as well as vectors, host cells, antibodies and recombinant methods for producing the polypeptides and polynucleotides.

BACKGROUND OF THE INVENTION

Eukaryotic cells are subdivided by membranes into multiple functionally distinct compartments that are referred to as organelles. Each organelle includes proteins essential for its proper function. These proteins can include sequence motifs often referred to as sorting signals. The sorting signals can aid in targeting the proteins to their appropriate cellular organelle. In addition, sorting signals can direct some proteins to be exported, or secreted, from the cell.

One type of sorting signal is a signal sequence, which is also referred to as a signal peptide or leader sequence. The signal sequence is present as an amino-terminal extension on a newly synthesized polypeptide chain A signal sequence can target proteins to an intracellular organelle called the endoplasmic reticulum (ER).

The signal sequence takes part in an array of protein-protein and protein-lipid interactions that result in translocation of a polypeptide containing the signal sequence through a channel in the ER. After translocation, a membrane-bound enzyme, named a signal peptidase, liberates the mature protein from the signal sequence.

The ER functions to separate membrane-bound proteins and secreted proteins from proteins that remain in the cytoplasm. Once targeted to the ER, both secreted and membrane-bound proteins can be further distributed to another cellular organelle called the Golgi apparatus. The Golgi directs the proteins to other cellular organelles such as vesicles, lysosomes, the plasma membrane, mitochondria and microbodies.

Only a limited number of genes encoding human membrane-bound and secreted proteins have been identified. Examples of known secreted proteins include human insulin, interferon, interleukins, transforming growth factor-beta, human growth hormone, erythropoietin, and lymphokines.

SUMMARY OF THE INVENTION

The present invention is based, in part, upon the discovery of novel human polynucleotide sequences and polypeptides encoded by these sequences. Polypeptides or synonymously proteins of the invention include an IL-17-like protein (clone 2191999), putative cell adhesion protein variants (clones

11753149.0.6 and 11753149.0.37), a putative surface membrane associated protein (clone 3883556 and the cDNA clone pCDNA3.1-TOPO-3883556-S54), PCK-1-like protein variants (clones 4301136-1 and 4301136-2), surface adhesion protein-like variants (clones 4324229 and 4324229-2), surface adhesion protein-like protein (AC012614_1.0.123), mitochondrial membrane- or plasma membrane-associated protein variants (clones 4339264-2 and 4339264-3), a putative microbody (peroxisome) associated protein (clone 4391184), and an opsonin-like and/or MAG4V-like protein and its cDNA variants (clones 4437909.0.4, 4437909.0.55 and cDNA TA-4437909-S443). Proteins of the invention include both the full length protein encoded by the open reading frame of the nucleic acid herein, as well as the processed mature form of the protein. Both the precursor and the mature forms of the proteins of the invention are described herein. These polynucleotides and the polypeptides encoded thereby are collectively referred to as the SECX gene set, the sequences of which are disclosed in SEQ ID NOs:1-31.

In one aspect, the invention includes an isolated SECX nucleic acid molecule which includes a nucleotide sequence encoding a polypeptide that includes the amino acid sequence of one or more of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 30. For example, in various embodiments, the nucleic acid can include a nucleotide sequence that includes SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29 and 31. Alternatively, the encoded SECX polypeptide may have a variant amino acid sequence, *e.g.*, have an identity or similarity less than 100% to the disclosed amino acid sequences, as described herein.

The invention also includes an isolated polypeptide that includes the amino acid sequence of one or more of SEQ ID NOs 2, 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28 or 30: or a fragment having at least 15 amino acids of these amino acid sequences. Also included is a naturally occurring polypeptide variant of a SECX polypeptide, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes under stringent conditions to a nucleic acid molecule consisting of a SECX nucleic acid molecule.

Also included in the invention is an antibody which selectively binds to a SECX polypeptide.

The invention further includes a method for producing a SECX polypeptide by culturing a host cell expressing one of the herein described SECX nucleic acids under conditions in which the nucleic acid molecule is expressed.

The invention also includes methods for detecting the presence and amount of a SECX polypeptide or nucleic acid in a sample from a mammal, *e.g.*, a human, by contacting a sample from the mammal with an antibody which selectively binds to one of the herein described polypeptides, and detecting the formation of reaction complexes including the antibody and the polypeptide in the sample. Detecting the formation of complexes in the sample indicates the presence of the polypeptide in the sample. Methods for measurements of antibody reaction complex concentrations are well known in the art. Methods for detecting and quantitating nucleic acids include hybridization and TaqMan™ quantitation.

The invention further includes a method for detecting or diagnosing the presence of a disease, *e.g.*, a pathological condition, associated with altered levels of a polypeptide having an amino acid sequence at least 80% identical to a SECX polypeptide in a sample. The method includes measuring the level of the polypeptide in a biological sample from the mammalian subject, *e.g.*, a human, and comparing the level detected to a level of the polypeptide present in normal subjects, or in the same subject at a different time, *e.g.*, prior to onset of a condition. An increase or decrease in the level of the polypeptide as compared to normal levels indicates a disease condition.

Also included in the invention is a method of detecting the presence of a SECX nucleic acid molecule in a sample from a mammal, *e.g.*, a human. The method includes contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule and determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample. Binding of the nucleic acid probe or primer indicates the nucleic acid molecule is present in the sample.

The invention further includes a method for detecting or diagnosing the presence of a disease associated with altered levels of a SECX nucleic acid in a sample from a mammal, *e.g.*. a human. The method includes measuring the level of the nucleic acid in a biological sample from the mammalian subject and comparing the level detected to a level of the nucleic acid present in normal subjects, or in the same subject at a different time. An increase or decrease in the level of the nucleic acid as compared to normal levels indicates a disease condition.

The invention also includes a method of treating a pathological state in a mammal, *e.g.*. a human, by administering to the subject a SECX polypeptide to the subject in an amount sufficient to alleviate the pathological condition. The polypeptide has an amino acid sequence at least 80% identical to a SECX polypeptide.

Alternatively, the mammal may be treated by administering an antibody as herein described in an amount sufficient to alleviate the pathological condition.

Pathological states for which the methods of treatment of the invention are envisioned include, by non-limiting example, cancer, a neoplastic disorder, an immune disorder, an immune deficiency, an autoimmune disease, acquired immune deficiency syndrome, transplant rejection, allergy, an infection by a pathological organism or agent, an inflammatory disorder, arthritis, psoriasis, a hematopoietic disorder, a skin disorder, a differentiative disorder, atherosclerosis, restenosis, a neurological disease or disorder, Alzheimer's disease, epilepsy, schizophrenia, tissue regeneration, trauma, a surgical or traumatic wound, a spinal cord injury, a corneal dystrophy, a reproductive disorder, a musculature disorder, and a skeletal disorder.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in

their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 provides the IL17-like nucleic acid sequence (SEQ ID NO:1) of clone 2191999 and the polypeptide (SEQ ID NO:2) encoded thereby.

FIG. 2 provides the nucleic acid sequence (SEQ ID NO:3) of clone 11753149.0.6 and the polypeptide (SEQ ID NO:4) encoded thereby.

FIG. 3 provides the nucleic acid sequence (SEQ ID NO:5) of clone 11753149.0.37 and the polypeptide (SEQ ID NO:6) encoded thereby.

FIG. 4 provides the nucleic acid sequence (SEQ ID NO:7) of clone 3883556 and the polypeptide (SEQ ID NO:8) encoded thereby.

FIG. 5 provides the nucleic acid sequence (SEQ ID NO:9) of clone 4301136-1 and the polypeptide (SEQ ID NO:10) encoded thereby.

FIG. 6 provides the nucleic acid sequence (SEQ ID NO:11) of clone 4301136-2 and the polypeptide (SEQ ID NO:12) encoded thereby.

FIG. 7 provides the nucleic acid sequence (SEQ ID NO:13) of clone 4324229 and the polypeptide (SEQ ID NO:14) encoded thereby.

FIG. 8 provides the nucleic acid sequence (SEQ ID NO:15) of clone 4324229-2 and the polypeptide (SEQ ID NO:16) encoded thereby.

FIG. 9 provides the nucleic acid sequence (SEQ ID NO:17) of clone AC012614_1.0.123 and the polypeptide (SEQ ID NO:18) encoded thereby.

FIG. 10 provides the nucleic acid sequence (SEQ ID NO:19) of clone 4339264-2 and the polypeptide (SEQ ID NO:20) encoded thereby.

FIG. 11 provides the nucleic acid sequence (SEQ ID NO:21) of clone 4357764-3 and the polypeptide (SEQ ID NO:22) encoded thereby.

FIG. 12 provides the nucleic acid sequence (SEQ ID NO:23) of clone 4391184 and the polypeptide (SEQ ID NO:24) encoded thereby.

FIG. 12 provides the nucleic acid sequence (SEQ ID NO:25) of clone 4437909.0.4 and the polypeptide (SEQ ID NO:26) encoded thereby.

FIG. 13 provides the nucleic acid sequence (SEQ ID NO:27) of clone 4437909.0.55 and the polypeptide (SEQ ID NO:28) encoded thereby.

FIG. 15 is a representation of a Western blot of h11753149 protein secreted by 293 cells.

FIG. 16 is a representation of a Western blot of h4437909 protein secreted by 293 cells.